

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Does liberalisation of cannabis policy influence levels of use in adolescents and young adults? A systematic review and meta-analysis
AUTHORS	Melchior, Maria; Nakamura, Aurélie; Bolze, Camille; Hausfater, Félix; El Khoury, Fabienne; Mary-Krause, Murielle; Azevedo Da Silva, Marine

VERSION 1 - REVIEW

REVIEWER	James White Cardiff University, UK
REVIEW RETURNED	05-Sep-2018

GENERAL COMMENTS	<p>Abstract</p> <ol style="list-style-type: none">Page 2, line 38: font size in outcome measuresPage 2, line 41: not clear why 30 days is defined as a sensitivity analysis when already listed in preceding sentence;Page 3: move sentence on changes in studies with a low risk of bias to be last sentence. Main result first then sensitivity; <p>Intro</p> <ol style="list-style-type: none">Consider a sentence or reference on associations between cannabis use and risk of psychosis, schizophrenia. Mendelian randomisation studies now suggest this association may be causal. Given costs of schizophrenia it warrants consideration. <p>Methods</p> <ol style="list-style-type: none">Page 7, line 24: justify exclusion of studies with only one measure of cannabis use;Page 9 line 3: justify use of statistical criterion on whether to use a fixed or random effects model. <p>Results</p> <ol style="list-style-type: none">Page 11, line 20: consider analysing all studies regardless of bias which can be meta-analysed, then comparing these findings to those you present on studies which only have a low bias. If there is a difference the bias can be somewhat quantified, if no difference it would suggest all studies could be combined. I realise this may have not been in your PROSPERO registration but you could classify these results as exploratory and declare they were not pre-planned;Figure 3B – consider removing all funnel plots when there are fewer than 10 studies as this can lead to a spurious conclusion;
-------------------------	---

	<p>9. Was any information provided on changes according to prevalence before change in policy? Discussion</p> <p>10. Consider tempering conclusions about legislation for recreational vs. other types of policy change. I don't think there are any direct comparisons made by individual studies.</p>
--	---

REVIEWER	Nicolas J. Schlienz, Ph.D. Johns Hopkins University School of Medicine United States of America
REVIEW RETURNED	19-Oct-2018

GENERAL COMMENTS	<p>The current report is a systematic review of studies evaluating the impact of cannabis decriminalization, liberalization of medical cannabis laws, and liberalization of recreational cannabis laws on adolescent and young adult use of cannabis. The systematic review is warranted given the continued rate of change to legislation governing the penalties for possession of cannabis (i.e., decriminalization), and legislation that pertain to medical and non-medical ("recreational") cannabis use. Overall, the manuscript is well-written and the authors have been extremely thorough in reporting the procedures used for the literature search as well as summarizing the results of the studies included in their review. The systematic review is particularly novel in that it seeks to evaluate specific aspects of reforms to cannabis legislation rather than a singular focus on studies of decriminalization, medical cannabis, or recreational cannabis. However, I have a number of concerns relative to aspects of the systematic review's methodology and summary of results.</p> <p>1. Comment (minor): While the authors sought to conduct both a systematic review and meta-analysis of the identified literature, the report seems to be better characterized as a systematic review given that significant study heterogeneity precluded the authors from conducting a meta-analysis for each of the three questions of interest (impact of decriminalization, impact of medical cannabis liberalization, impact of recreational cannabis liberalization). The title of the paper lists the report as a systematic review and the study design is listed in the abstract as a systematic review and meta-analysis. The authors should reconcile this discrepancy.</p> <p>2. Comment (minor): Though the abstract is well-written and nicely assembled, there is a rather strong emphasis on summarizing the subtle details of the literature search strategy, and in contrast, a smaller summary of the results that were culled from the studies that the authors included in the systematic review. The abstract may be strengthened by including more information about the results and corresponding implications.</p> <p>3. Comment (minor): The authors may wish to highlight their focus on decriminalization, medical cannabis liberalization, and recreational cannabis liberalization as a study strength (for the strengths and limitations listed on p.4). In fact, focusing on these three domains sets it apart from Sarvet et al.'s recent systematic review and meta-analysis (2018) of medical cannabis laws and adolescent cannabis use.</p>
-------------------------	--

	<p>4. Comment: Given that many readers will not necessary have public policy backgrounds, I really appreciated how the authors provided explicit definitions for decriminalization and legalization.</p> <p>5. Comment (minor, p. 5): Given the near-constant evolution of reforms to cannabis laws, it may be useful for the authors to indicate the month and year when they wrote the systematic review and meta-analysis to provide additional context for the countries and states (in the U.S.) that currently permit medical or non-medical cannabis use.</p> <p>6. Comment (pp. 5-6): While the current report already includes more than 70 cited references, the introduction is particularly light on citations. For example, the authors do not include citations to support the following sentence: "For cannabis users, decriminalized or regulated access to the substance decreases the criminal and legal risk incurred." In other instances, the authors may wish to add caveats to their summary of portions of the adult literature given how some of the results are limited to single studies (i.e., "In adults, the liberalization of cannabis policy has been followed by increases in levels of heavy cannabis use.").</p> <p>7. Comment (p. 6): The stated objective of the current report is to summarize how cannabis decriminalization, medical legalization, and recreational legalization may affect adolescent and young adults' cannabis use. However, the rationale for exploring cannabis use among adolescents and young adults is limited to a few sentences. While the authors don't need to provide a lengthy rationale for focusing on this special population, this section could be improved by further elaborating on the potential implications of decriminalization and both medical and non-medical legalization.</p> <p>8. Comment (pp. 6-9): Details of the search strategy and inclusion criteria are clear and concise.</p> <p>9. Comment (minor, p. 7): Why did the authors conduct a risk of bias assessment? Adding a sentence at the beginning of this section would clarify the rationale for this important procedure.</p> <p>10. Comment (minor, p. 8): In discussing the process of data extraction, the authors indicate that a coding sheet included several study variables including 'setting' and 'inclusion criteria/number of subjects (ns)' among others, and are used as column headings in Tables 1-3. 'Setting' is somewhat ambiguous and it may be useful to change 'Inclusion criteria' to 'Sample or participant characteristics.' Similarly, 'cannabis use measure' is also slightly confusing since it appears to characterize the duration of the time window for assessing cannabis use as opposed to the approach or measure used to assess frequency or quantity of cannabis use (e.g., Timeline Followback).</p> <p>11. Comment (p. 9): In describing calculation of the statistic to calculate the presence of between-study heterogeneity (I squared), are there recommended cutoffs in order to compute meta-analytic calculations? It seems that this statistic is not always reported in meta-analyses. The authors also cite how values > 50% indicated significant heterogeneity and they provide meta-analytic data for the section on pp. 13-14 that focuses on legalization of recreational cannabis despite an I-squared value of</p>
--	--

	<p>64.4%. Yet, meta-analytic data are not provided for the sections summarizing decriminalization (I-squared=99.5%) and medical cannabis (I-squared=98.6%). If meta-analytic results are reported for recreational cannabis despite an I-squared value that exceeds 50%, why not also compute meta-analytic data for decriminalization and recreational cannabis studies but add a caveat about between-study heterogeneity?</p> <p>12. Comment (p. 9): It is not clear why the authors chose certain values for planned subgroup analyses. Please include the rationale or justification for study year (less than 2000 or greater than or equal to 2000), participant's age (less than or greater than or equal to age 18), etc., etc.</p> <p>13. Comment (pp. 9-10): Much of the results pertaining to various stages of the literature search strategy are not nearly as important as the actual results of the articles that are included in the systematic review. Further, much of this information is redundant with what is presented in Figure 1 and included in some of the subheadings of Tables 1-3.</p> <p>14. Comment (pp. 11-14): In summarizing the results for studies that examined the impact of decriminalization (which are listed in Table 1), some of these studies are quite old (i.e., Johnston et al., 1981; Thies & Register, 1993, McGeorge & Aitken, 1997, etc.). In contrast, the vast majority of studies listed in Table 2 (medical cannabis legalization) and Table 3 (recreational cannabis legalization) are more recent. Though the investigations of decriminalization were not characterized as having a very low risk of bias, do the authors have any concerns about the generalizability of findings for work that was published outside of the past decade?</p> <p>15. Comment (p. 15): The strengths and limitations section of the review is well thought-out, clear, and nicely written.</p> <p>16. (pp. 18-19): The language used in the section detailing the implications of decriminalization, medical cannabis legalization, and recreational cannabis legalization seems appropriate given the very modest number of studies that the authors characterized as having a very low risk of bias. Consequently, it seems quite difficult to make strong inferences about the long-term impact of cannabis decriminalization and cannabis legalization given various study methodologies and considerable between-study heterogeneity. With these limitations and concerns, do the authors have any specific recommendations or suggestions for how future work evaluating the impact of decriminalization and policy reform can be improved upon?</p>
--	--

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Abstract

1. "Page 2, line 38: font size in outcome measures"

We apologize for this error which has been fixed.

2. "Page 2, line 41: not clear why 30 days is defined as a sensitivity analysis when already listed in preceding sentence."

Since the text was reformatted, as per the Editor's request, this text no longer appears in the abstract.

3. "Page 3: move sentence on changes in studies with a low risk of bias to be last sentence."
As requested, this sentence was moved.

Introduction

5. "Page 7, line 24: justify exclusion of studies with only one measure of cannabis use."

To address this issue, we added the following text (page 7):

'[studies] not including at least two measures of cannabis use and which did not make it possible to compare changes between before and after policy change'

6. "Page 9 line 3: justify use of statistical criterion on whether to use a fixed or random effects model."
Actually, there is no strict statistical criterion to decide on whether or not to use a random effects model. We first conducted a fixed effects model and given the high level of heterogeneity that was observed ($I^2 > 99\%$ for decriminalisation and legalisation of cannabis), a random effects model was applied.

Results

7. "Page 11, line 20: consider analyzing all studies regardless of bias which can be meta-analysed, then comparing these findings to those you present in studies which only have a low bias."

Meta-analyses were conducted including all studies, regardless of the potential level of bias. In additional analyses, we confirmed that our results were stable when only studies that were not characterised by probable or high bias were considered. This was clarified in the text (page 11):
'Given the small number of articles in each category, all studies except those with a high level of bias were meta-analysed. In additional analyses, we verified that findings were stable when studies characterised by probable bias were excluded.'

8. "Figure 3b – consider removing all funnel plots when there are fewer than 10 studies as this can lead to a spurious conclusion."

The funnel plot was removed, as requested.

9. "Was any information provided on changes according to prevalence before change in policy?"
Unfortunately, there was no such information in the studies we examined.

Discussion

10. "Consider tempering conclusions about legislation for recreation vs. other types of policy change."
As requested, we tempered the conclusion, which now reads (page 19):

'Legalisation of use for recreational purposes appears to possibly result in a small increase.'

Reviewer 2

1. "The title of the paper lists the report as a systematic review and the study design is listed in the abstract as a systematic review and meta-analysis. The authors should reconcile this discrepancy."
As requested, we now indicate in the title that we conducted a systematic review

2. "The abstract may be strengthened by including more information about the results and corresponding implications."

To address this comment, we added the estimated difference in levels of cannabis use in youths after legalisation of use for recreational purposes.

3. "The authors may wish to highlight their focus on decriminalization, medical cannabis liberalization, and recreational cannabis liberalization as a study strength ([...] p. 4).

We thank the reviewer for this suggestion and have added the following text to the 'Strengths and limitations' paragraph (page 4):

'To date, this is the first study to attempt to summarise research on the consequences of various types of changes in cannabis laws and policies (decriminalisation as well as different forms of legalisation) with regard to patterns of use among adolescents and young adults.'

4. "Given than many readers will not have public policy backgrounds, I really appreciated how the authors provided explicit definitions for decriminalization and legalization."

We thank the reviewer for this comment.

5. "Given the near-constant evolution of reforms to cannabis laws, it may be useful for the authors to indicate the month and year when they wrote the systematic review and meta-analysis to provide additional context for the countries and states (in the U.S.) that currently permit medical or non-medical cannabis use.'

We added to the abstract that the systematic review and meta-analysis were carried out by March 1st, 2018.

6. "The introduction is particularly light on citations. [...] The authors may wish to add caveats to their summary of portions of the adult literature given how some of the results are limited to single studies."

As requested, we added references to the part of the introduction focusing on changes in cannabis laws and levels of use among adults (page 6).

7. "[...] The rationale for exploring cannabis use among adolescents and young adults is limited to a few sentences. While the authors don't need to provide a lengthy rationale for focusing on this special population, this section could be improved by further elaborating on the potential implications of decriminalization and both medical and non-medical legalization".

To address this comment, we added the following to our study rationale (page 6):

'Youths are a high risk group in terms of illegal substance use and may be especially sensitive to changes in policy; at the same time they may also be especially vulnerable to the biological, psychological and behavioural consequences of cannabis.'

8. "Details of the search strategy and inclusion criteria are clear and concise."

We thank the reviewer for this remark.

9. "Why did the authors conduct a risk of bias assessment? Adding a sentence at the beginning of this section (page 7) would clarify the rationale for this important procedure."

We added to the text (page 7) that risk of bias analysis was conducted 'In order to judge the quality of studies that were analysed'.

10. "In discussing the process of data extraction, the authors indicate that a coding sheet including 'setting' and 'inclusion criteria/number of subjects' among others, and are used as a column headings in Tables 1-3. 'Setting' is somewhat ambiguous and it may be useful to change 'Inclusion criteria' to 'Sample or participant characteristics'. Similarly, 'cannabis use measure' is also slightly confusing since it appears to characterize the duration of the time window for assessing cannabis use as opposed to the approach or measure used to assess frequency or quantity of cannabis use."

As requested, we changed column labels in all three tables to: 'Place of study'; 'Participant characteristics', 'Cannabis use measure (frequency/period). This is also now indicated in the Methods section (page 8).

11. "In describing calculation of the statistic to calculate the presence of between-study heterogeneity (I squared), are there recommended cutoffs in order to compute meta-analytic calculations? It seems that this statistic is not always reported in meta-analyses. The authors also cite how values of >50% indicate significant heterogeneity and they provide meta-analytic data for the section on pp. 13-14 that focuses on legalization of recreational cannabis despite an I-squared value of 64.4%. [...] Why not also compute meta-analytic data for decriminalization and recreational cannabis studies but add a caveat about between-study heterogeneity?"

The I² statistic serves to examine whether the studies included in a meta-analysis are consistent or not. If they are not, there is no point in meta-analysing them because the risk of error is too large. While there is no official cut-off to determine a level of heterogeneity that is low, an I² of 50% is considered ideal. Actually, there was a mistake in the results we initially reported, the I² of the meta-analysis focusing on legalisation of recreational cannabis, which is 45.0%. The text was modified (page 9):

'an I² ≤ 50% is generally considered to indicate low heterogeneity'

As indicated in the supplementary file, we did conduct meta-analyses for all three policy changes examined.

12. "It is not clear why the authors chose certain values for planned subgroup analyses. Please include the rationale or justification for study year (less than 2000 or greater than or equal to 2000), participant's age, etc."

We now explain how cutoffs for subgroup analyses were determined (page 9):

'For each type of cannabis policy change, we also performed a priori hypothesised subgroup analyses, according to study design (cohort vs. cross-sectional, to account for differences in study design), study year (< 2000 vs. ≥ 2000 to discriminate between early vs. late studies), participants' age (< vs. ≥ 18 years to discriminate between participants who were legally responsible or not) and the measure of cannabis use (30-day use vs. 12-month use to discriminate between recent vs. less recent cannabis use).'

13. "Much of the results pertaining to various stages of the literature search strategy (pp. 9-10) are not nearly as important as the actual results of the articles that are included in the systematic review. Further, much of this information is redundant with what is presented in Figure 1 and included in some of the subheading of Tables 1-3.

As requested, we simplified and cut down the text presenting the literature search strategy.

14. "In summarizing the results of studies that examined the impact of decriminalization (Table 1), some of the studies are quite old. In contrast, the vast majority of studies listed in Table 2 (medical cannabis legalization) and Table 3 (recreational cannabis legalization) are more recent. [...] Do the authors have any concerns about the generalizability of findings for work that was published outside the past decade?"

The reviewer raises an important point. To account for this phenomenon, as indicated on page 9, we conducted additional analyses stratifying on the year in which the study was conducted. As indicated page 12, the results did not seem to vary between studies conducted 2000 < vs. ≥2000.

15. "The strength and limitations section of the review is well thought-out, clear, and nicely written." We thank the reviewer for this comment.

16. "It seems quite difficult to make strong inferences about the long-term impact of cannabis decriminalization and cannabis legalization given various study methodologies and considerable between-study heterogeneity. With these limitations and concerns, do the authors have any specific recommendations or suggestions for how future work evaluating the impact of decriminalization and policy reform can be improved upon?"

Following this systematic review of the literature, it seems that future work should systematically evaluate changes in cannabis legislation, using both cross-sectional as well as longitudinal samples, in all settings where such changes occur. The following text was added to the study conclusion (page 19):

'Repeated cross-sectional as well as longitudinal studies will be necessary to thoroughly evaluate adolescents' levels of cannabis use following changes in policy.'

VERSION 2 – REVIEW

REVIEWER	James White Cardiff University, Wales, United Kingdom
REVIEW RETURNED	23-Nov-2018

GENERAL COMMENTS	The reviewers have addressed the comments.
-------------------------	--